

CLAIMS

- 5 1- A molecule comprising three segments :
- a targeting segment C capable of binding to the membranes of cells engaged in an apoptosis process ;
 - a therapeutic segment A comprising a biologically active compound ; and
 - a linker segment L between the targeting segment and the therapeutic segment,
- 10 said linker segment L being cleavable in vivo in the environment of a tissue or of a cell in apoptosis.
- 2- The molecule according to claim 1, wherein said linker segment L comprises a chemical function recognised and cleaved by an enzyme or a set of enzymes specific to the
- 15 environment of the targeted cells.
- 3- The molecule according to claim 1 or 2, wherein said linker segment L comprises a sequence recognised and cleaved by a protease present by majority in the targeted tissue, more particularly selected from a metalloprotease of the extracellular matrix, a urokinase,
- 20 and a protease specific to the cleaving of the extracellular segment of the membranous cytokines or of their receptors.
- 4- The molecule according to any of claims 1 to 3, wherein said linker segment L comprises a sequence selected in that it contains at least one B1-B2 residue couple given in
- 25 the following table :

| B ₁ | B ₂ |
|-----------------|----------------|
| Val/Ala/Leu/Met | X |
| Leu/Tyr/Phe | X |
| Ala | Leu |
| Leu | Val |
| Val | Cys |
| Gly | Leu/Ile |

| | |
|---|-----------------------------|
| Gly | Val |
| Ala | Val |
| Asn | Val |
| Arg | Phe |
| Gly/Ala/Asn/Glu/Gln/Pro/Arg/His/Asn | Hydrophobes, natural or not |
| Polar : Arg/Asp/Glu/Gln/Thr/Asn Hydrophobe : Ala | Hydrophobes, natural or not |

wherein X is any amino acid residue, natural or not.

5- The molecule according to any of the preceding claims, wherein said targeting segment
5 C is capable of binding to the membranes comprising lipids, the total electrostatic charge of which is negative, in particular phosphatidylserine.

6- The molecule according to any of the preceding claims, wherein said targeting segment comprises the following peptidic sequence :

10 J¹-J²-J³-J⁴-J⁵-J⁶-Z⁷-U⁸-J⁹-J¹⁰-U¹¹-R-J¹³-J¹⁴-U¹⁵-K-G-X¹⁸-G-T-J²¹-E-J²³-J²⁴-U²⁵-J²⁶-J²⁷-
J²⁸-U²⁹-J³⁰-J³¹-R-J³³-J³⁴-J³⁵-J³⁶-B³⁷-J³⁸-J³⁹-U⁴⁰-J⁴¹-J⁴²-J⁴³-U⁴⁴-J⁴⁵-J⁴⁶-J⁴⁷-J⁴⁸-J⁴⁹-R-J⁵¹-U⁵²-
J⁵³-J⁵⁴-D-U⁵⁶-K-S-Z⁵⁹-L-J⁶¹-J⁶²-J⁶³-J⁶⁴-Z⁶⁵-J⁶⁶-J⁶⁷-U⁶⁸-J⁶⁹-J⁷⁰-J⁷¹-U⁷²-J⁷³-J⁷⁴-J⁷⁵-J⁷⁶

(S1)

wherein J, Z, U, X, and B represent amino acids such that :

- 15 - the J amino acids are selected independently of one another from the natural amino acids, or from derivatives thereof, such that at least 50 % of them are polar residues selected from R, N, D, C, Q, E, G, H, K, Orn, P, S, T and Y,
- the U amino acids are selected from A, C, G, I, L, M, F, W, Y, and V,
- amino acid X¹⁸ is selected independently of the other amino acids of the sequence
20 from A, N, C, Q, G, H, I, L, M, F, S, T, W, Y and V,
- amino acid B³⁷ is selected independently of the other amino acids of the sequence from R, A, C, G, I, L, M, F, W, Y, and V,
- amino acid Z⁷ is selected independently of the other amino acids of the sequence from D and E,
25 - amino acids Z⁵⁹ and Z⁶⁵ are selected independently from E, D, K, and R,
the exponents indicating the position of the amino acids in the sequence.

7- The molecule according to claim 6, wherein amino acids U and B are selected according to one of the examples given below :

| | U ⁸ | U ¹¹ | U ¹⁵ | U ²⁵ | U ²⁹ | B ³⁷ | U ⁴⁰ | U ⁴⁴ | U ⁵² | U ⁵⁶ | U ⁶⁸ | U ⁷² |
|------|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Ex 1 | V | L | M | I | L | R | I | Y | L | L | V | L |
| Ex 2 | A | I | I | I | L | R | I | Y | L | L | I | L |
| Ex 3 | A | I | I | I | L | R | I | Y | L | L | M | V |
| Ex 4 | A | L | M | L | L | R | I | Y | L | L | I | M |
| Ex 5 | A | L | M | I | I | R | V | Y | L | L | I | M |
| Ex 6 | A | L | M | I | I | R | I | F | L | L | I | M |
| Ex 7 | A | L | M | I | V | R | I | F | L | L | I | F |
| Ex 8 | V | L | M | I | L | R | I | F | L | L | I | M |
| Ex 9 | A | L | M | I | L | R | I | F | L | L | I | M |
| Ex10 | A | L | M | I | L | R | I | Y | L | L | A | A |
| Ex11 | V | L | M | I | L | R | I | Y | L | L | V | L |
| Ex12 | V | L | M | I | L | R | I | F | L | L | V | L |

8- The molecule according to any of the preceding claims, wherein said targeting segment C comprises a sequence selected from the group consisting of sequences SEQ ID Nos 23-32.

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9- The molecule according to any of claims 1-5, wherein said targeting segment C comprises the sequence of all or part of an annexin, of a C1 or C2 type domain of the blood coagulation factors, of a domain V of a protein of the family of 2-Glycoproteins-I, of a FYVE type domain, of a PH type domain, or a fragment or a derivative having at least 50 % of identity.

10- The molecule according to claim 9, wherein said targeting segment C comprises a sequence selected from sequences SEQ ID Nos 1-16 and 17-22, preferably SEQ ID Nos 2-4, 6-8, 10-12, 14-16 and 19-22 or a fragment thereof.

15

11- The molecule according to any of the preceding claims, wherein said therapeutic segment A has anti-tumoral activity.

12- The molecule according to claim 11, wherein said therapeutic segment A is selected from the group consisting of a molecule of the family of TNF α or derivatives thereof (TRAIL-Do), a human IL4 molecule or one of its isoforms, a molecule of the family of

anthracyclines or one of its active derivatives, preferably doxorubicin, a taxane molecule such as paclitaxel or docetaxel or one of its active derivatives, a methotrexate molecule or one of its active derivatives, 2-methoxyestradiol or one of its active derivatives, molecules of the family of antiprimidines such as cytosine arabinoside or difluorodesoxycytidine or
 5 one of their active derivatives, molecules of the family of alkylating agents derived from nitrogen mustards such as phenylalanine mustard (Melphalan) or a derivative such as Chlorambucyl.

13- The molecule according to any of claims 1-10, wherein said therapeutic segment A has
 10 anti-inflammatory activity.

14- The molecule according to claim 13, wherein said therapeutic segment A is selected from the group consisting of an N-terminal segment of human annexin I, in particular NTA1, anti-inflammatory cytokines, and in particular IL10 and IL13 or one of their
 15 appropriate mutants, the non-activating inhibitors of the membranous receptors of pro-inflammatory cytokines such as in particular the inhibitor of the IL1 receptor or an appropriate mutant of this inhibitor, glucocorticoids, non-steroid anti-inflammatories or their derivatives considered to be inhibitors of cylo-oxygenase enzymes 1 and 2, and Methotrexate, an inhibitor of the membranous receptors of the family of TNFR, in
 20 particular peptides containing at least the corresponding CRD1 extracellular domain.

15- A pharmaceutical composition comprising a molecule according to any of the preceding claims.

25 16- The use of a molecule according to any of claims 1-14 for manufacturing a medication.

17- The use of a molecule according to claim 11 or 12 for manufacturing a medication intended for cancer treatment.

30 18- The use of a molecule according to claim 13 or 14 for manufacturing a medication intended for the treatment of an inflammatory disease.